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Microcontainers for oral vaccine delivery

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Purpose

To fabricate devices in micrometer size (microcontainers) in SU-8 by two-steps of photolithography, and to load these microcontainers with a powder of vaccine using an embossing method. Furthermore, this system was investigated as an oral delivery system for vaccines.

Introduction

Delivery of vaccine is often done by injection, but it would be much more convenient for the patients, if the vaccines could be dosed as a tablet via the oral route. For being able to deliver the vaccine by the oral route, a combination of an antigen, adjuvant and a particulate system is necessary. An example of such a particulate system is cubosomes. Cubosomes are highly twisted, continuous lipid bilayers with two congruent, non-intersecting water channels providing both hydrophilic and hydrophobic domains and a large surface area for associations of antigens and adjuvants [1].

For delivering vaccines by the oral route, micro fabricated drug delivery devices can be used. Of these micro devices, microcontainers are suggested as especially promising [2], [3]. Primarily, this is due to the fact that the size and shape of the microcontainers can be controlled very precisely. Microcontainers are polymeric, cylindrical devices in the micrometer size range (Figs 1). A potential advantage of microcontainers is that these devices allow for unidirectional release, as only one side of the microcontainers is open compared to conventional particles where release occurs from the whole surface [2]. The microcontainers have been suggested as a potential approach to improve the oral bioavailability of drugs [4] as they are able to protect the drug or vaccine through the stomach and bring it to the intestine, where the drug or vaccine should be released and absorbed.

Results

The fabrication of microcontainers resulted in devices with an inner diameter of 220 μm and a cavity depth of 270 μm (Figs 1). A vaccine powder was produced by the method of spray drying, where a solution of lipid (Dimodan[®]), antigen (ovalbumin) and adjuvant (quil-A) in ethanol and water was sprayed into a powder. Subsequently, the powder was suspended in water to obtain particles with a cubic structure (defining the cubosomes). The formation of cubosomes was verified using cryo-TEM (Figs 2). The size of the particles in water was measured by dynamic light scattering and resulted in a size of 233 ± 13 nm.

After *in vitro* characterisation, the cubosome powder was loaded into SU-8 microcontainers using a powder embossing method. Here, a shadow mask was aligned onto the cavity of the microcontainers (sitting on a silicon chip), and the microcontainers with the shadow mask were then pressed into the powder of cubosomes (Figs 3). This resulted in filled microcontainers, and this was verified using scanning electron microscope (SEM) and x-ray microtomography (Figs 4).

After loading the microcontainers with the powders, a lid of the pH sensitive polymer Eudragit L100-55 was deposited on the cavity of the microcontainers by a spray coating system. This can protect the vaccine inside the microcontainers through the stomach and provide a release of the vaccine powder in the intestine. The vaccine-filled and coated microcontainers are currently being tested in mice to evaluate the *in vivo* effect of this oral vaccine delivery system.

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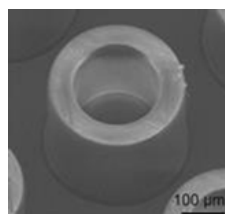


Figure 1: SEM image of a SU-8 microcontainer

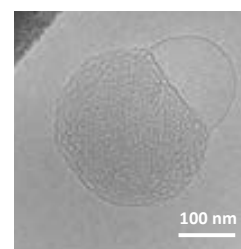


Figure 2: Cryo-TEM image of a cubosome particle suspended in water.

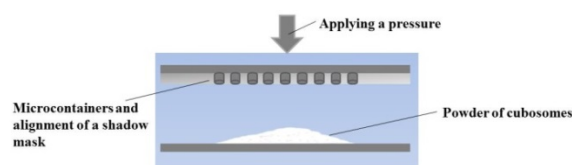


Figure 3: Drawing of the powder embossing method for loading of the microcontainers with the powder of cubosomes for vaccine delivery.

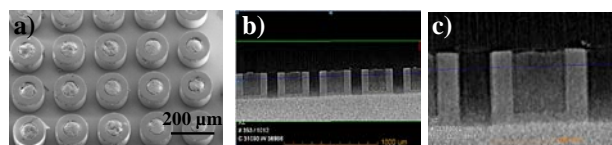


Figure 4: Loading of the microcontainers with cubosomes. a): SEM image of the loaded microcontainers, and b) & c): x-ray microtomography images of the loaded microcontainers.